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# Stereospecific Ring Contraction of Bromocycloheptenes through Dyotropic Rearrangements via Nonclassical Carbocation–Anion Pairs

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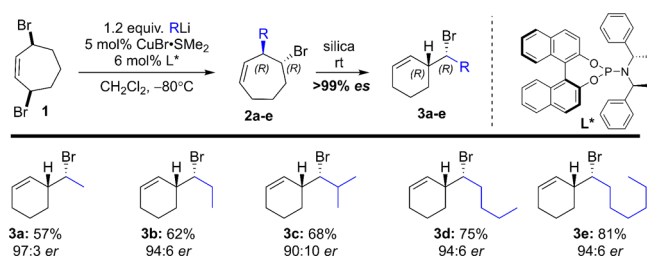
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## Supporting Information

**ABSTRACT:** Experimental and theoretical evidence is reported for a rare type I dyotropic rearrangement involving a [1,2]-alkene shift, leading to the regio- and stereospecific ring contraction of bromocycloheptenes. This reaction occurs under mild conditions, with or without a Lewis acid catalyst. DFT calculations show that the reaction proceeds through a nonclassical carbocation–anion pair, which is crucial for the low activation barrier and enantiospecificity. The *chiral* cyclopropylcarbinyl cation may be a transition state or an intermediate, depending on the reaction conditions.

In the course of our investigation of the desymmetrization of *meso*-3,7-dibromocycloheptene **1**, we discovered that the initially formed enantiomerically enriched homoallylic bromides **2** were spontaneously isomerized with retention of configuration to form chiral substituted cyclohexenes **3** (Scheme 1).<sup>1</sup> This reaction could be accelerated by Lewis

## Scheme 1. Desymmetrization of **1** by AAS and Subsequent Rearrangement of Cycloheptenes **2** to Cyclohexenes **3**<sup>a,b</sup>

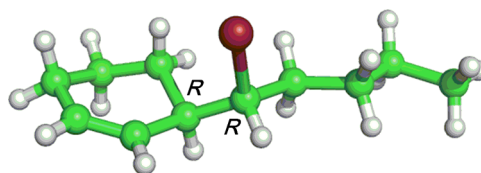


<sup>a</sup>Isolated yields over two steps. <sup>b</sup>er's of **2a–e** and **3a–e** were determined by chiral GC to be the same, so *es* is >99%.

acids such as silica or ZnBr<sub>2</sub>, with no change in stereoselectivity. We have studied this reaction by a combination of experiments and computations, and now report that this involves a rare dyotropic rearrangement involving nonclassical cyclopropylcarbinyl cations on the reaction paths as either transition states or intermediates, depending on the conditions.

The copper-catalyzed desymmetrization of **1** by asymmetric allylic substitution<sup>2</sup> (AAS) with organolithium reagents<sup>3</sup> initially afforded the expected products **2a–e** (>99:1 *dr*), as observed by NMR spectroscopy of the crude reaction mixtures [see Supporting Information (SI)]. The reaction also proceeded with high enantioselectivity, as determined by chiral GC.<sup>1</sup> However, upon exposure to silica, the bromocycloheptenes **2a–e** isomerized to afford six-membered cyclic homoallylic bromides **3a–e**. The ring contraction reaction proceeded with complete regioselectivity and enantiospecificity, as determined by chiral GC [see SI, part 1 and SI, part 2].

In fact, the rearrangement reaction was so facile that the transformation from cycloheptenes **2a–e** to cyclohexenes **3a–e** occurred even on neutral alumina, or when left standing in chloroform-*d* (*t*<sub>1/2</sub> ≈ 6 days). The major enantiomer of **3d**,<sup>4</sup> obtained as a colorless oil, was determined to be (*R,R*) by X-ray crystallography using only 5 μg of compound and the crystalline sponge method developed by the Fujita group<sup>5</sup> (Figure 1). A similar attempt was made to study the absolute



**Figure 1.** Ball-and-stick representation of the X-ray structure of **3d** determined by the crystalline sponge method.

configuration of its precursor **2d**; however, the rearrangement occurred while soaking in crystalline sponge, and only **3d** was detected when the X-ray analysis was performed.

The ring contraction reaction from **2a–e** to **3a–e**, interconverting the two isomeric homoallylic bromides, involves the 1,2-positional exchange of the alkenyl and bromo groups; thus it is formally a [2,2]-dyotropic rearrangement. These were first described in 1972 by M. T. Reetz as a class of pericyclic valence isomerizations involving the simultaneous

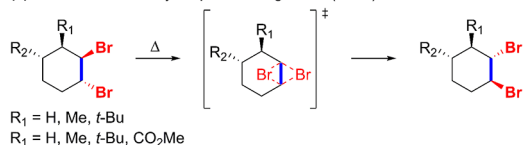
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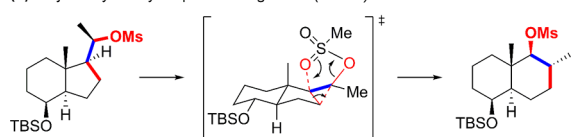
intramolecular migration of two  $\sigma$ -bonds.<sup>6,7</sup> Type I dyotropic rearrangements occur when the two migrating groups exchange their positions (e.g., the classic rearrangement of *anti* vicinal dibromides, Scheme 2a),<sup>8</sup> while in type II rearrangements the

### Scheme 2. Uncatalyzed Concerted Type I Dyotropic Rearrangements Occurring on a Static C–C Scaffold

(a) Vicinal dibromide dyotropic rearrangement (Ref 8)



(b) Alkyl-mesylate dyotropic rearrangement (Ref 20)



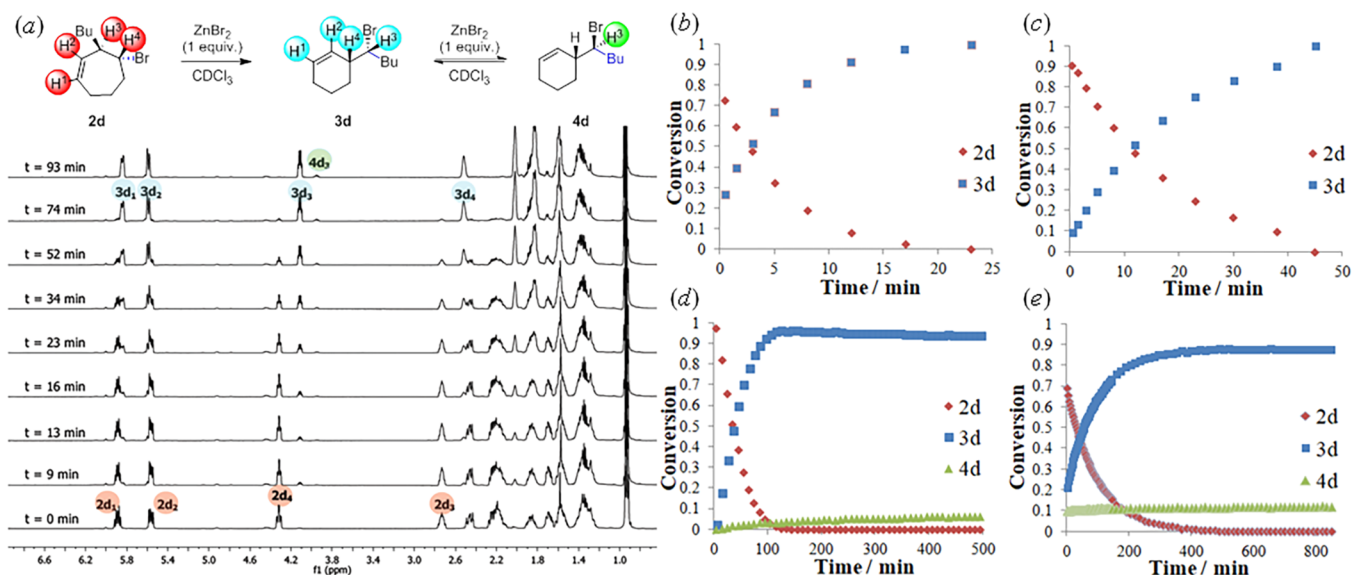
groups migrate to entirely different positions. Dyotropic reactions have become more common recently in organic and organometallic chemistry<sup>9</sup> and have even been applied to total syntheses.<sup>9,10</sup> The concerted migration of carbon chains through a [2,2]-shift on a static C–C scaffold is uncommon. [ $\sigma_2$  +  $\sigma_2$ ] processes are thermally forbidden by the Woodward–Hoffmann rules,<sup>11,12</sup> but the reaction becomes allowed if one migrating group has a lone pair and migrates with inversion. Nevertheless, such reactions are still rare because the activation barriers are usually quite high.<sup>13</sup>

Until recently, the only experimental examples of such reactions involved highly strained lactones reacting under strenuous conditions. Examples of alkyl group migration are the ring expansion of  $\beta$ -lactones to butyrolactones promoted by stoichiometric magnesium bromide,<sup>14–16</sup> or the rearrangement of cage  $\delta$ -lactones to  $\gamma$ -lactones at 350 °C on a quartz column.<sup>17</sup> Acyl group migration involving a  $\beta$ -lactone ring expansion

promoted by stoichiometric Lewis acid is also known.<sup>18</sup> In recent years, milder dyotropic rearrangements have been discovered. Gutta and Tantillo proposed a 1,2-positional exchange of an alkyl group and a hydrogen atom in their computed biosynthetic pathway for formation of pentalenene in 2006.<sup>19</sup> More recently, Faza, Lopez, and co-workers reported the type I dyotropic ring expansion of hydrindane to decalin occurring at –78 °C upon mesylation (Scheme 2b).<sup>20</sup> To the best of our knowledge, a concerted and uncatalyzed type I dyotropic migration of a C–C  $\pi$  system is still unknown.

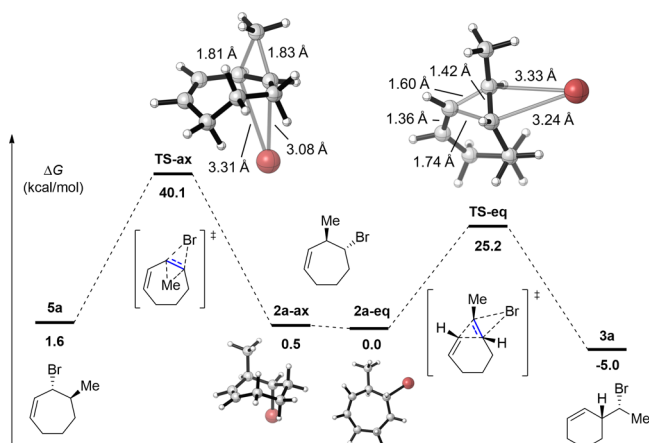
The mechanism of this rearrangement was investigated by NMR spectroscopy. Time-dependent aliquot studies with silica as reagent (500% w/w) for the rearrangement of bromocycloheptene **2d** showed that bromocyclohexene **3d** (>99% *es*) was the only product generated. This was observed in both polar aprotic (chloroform-*d*) and apolar (benzene-*d*<sub>6</sub>) solvents, although the rate of reaction was slower in benzene-*d*<sub>6</sub> (Figure 2b,c); the lack of solvent dependence for selectivity indicates that the reaction does not proceed through a discrete carbocation. The use of Lewis acids (e.g., ZnBr<sub>2</sub> and TMSOTf) led to poorer selectivity in the rearrangement reaction, with ca. 5–10% of a different diastereoisomer **4d** observed (Figure 2d,e);<sup>21</sup> its formation may be explained by the ionization of product **3d** by the stronger Lewis acids [see SI]. There was, fortunately, no erosion in *ee* of the expected product. These reactions with Lewis acids could be monitored *in situ* by NMR time course experiments in either chloroform-*d* (Figure 2a) or benzene-*d*<sub>6</sub> with no difference in product ratio or enantiospecificity, although the reaction was always slower in the apolar solvent [see SI]. The reaction could also be performed with Brønsted acids [see SI], or with catalytic amounts of Lewis acids (Figure 2e), albeit at a much reduced rate. When conducted in the presence of radical scavenger BHT (1.0 equiv), the reaction profile did not change [see SI], indicating that a radical pathway was not involved.

To further understand the mechanism and specificity of the rearrangement, we performed DFT calculations on compound



**Figure 2.** Left: (a) <sup>1</sup>H NMR spectroscopic profiles of bromocycloheptene **2d** with ZnBr<sub>2</sub> (1 equiv) in chloroform-*d* with increasing time; reaction scheme is shown at top. Right: Reaction progress of **2d** with silica (500% w/w) monitored by timed aliquots in (b) chloroform-*d* and (c) benzene-*d*<sub>6</sub>. Reaction progress of **2d** monitored by *in situ* NMR spectroscopy with (d) ZnBr<sub>2</sub> (1 equiv) in chloroform-*d* and (e) TMSOTf (0.5 equiv) in chloroform-*d*.

**2a** at the M06-2X/6-311+G(d,p)//M06-2X/6-31G(d) level of theory,<sup>22</sup> using Gaussian 09.<sup>23</sup> The SMD solvation model<sup>24</sup> for CHCl<sub>3</sub> was used throughout. Computed structures were visualized using CYLview.<sup>25</sup> We first investigated whether a concerted uncatalyzed dyotropic rearrangement is plausible. The cycloheptene ring of **2a** has two low-energy conformations, where the methyl and bromo substituents are either pseudoaxial (**2a-ax**) or pseudoequatorial (**2a-eq**). From **2a-eq**, a dyotropic rearrangement involves the experimentally observed 1,2-shift of both the alkenyl and bromo groups to form **3a**. The barrier for this transformation is only 25.2 kcal/mol (Figure 3), and the reaction is exergonic by 5.0 kcal/mol.

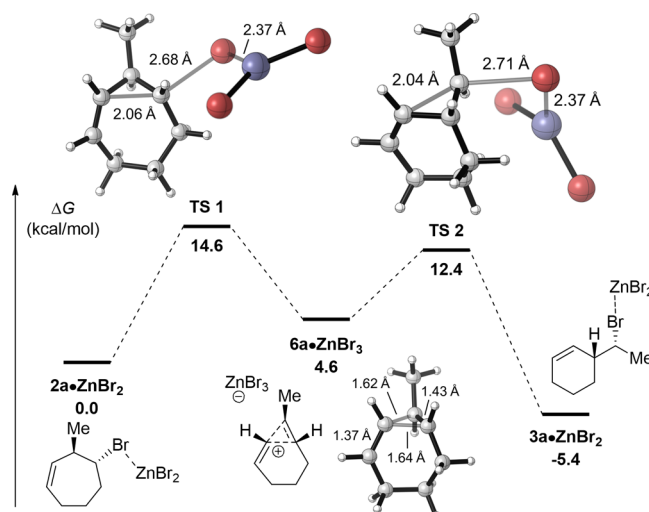


**Figure 3.** Calculated free energy profile for the concerted dyotropic rearrangements from the pseudoaxial (left part) or pseudoequatorial (right part) conformations of **2a**.

In contrast, the dyotropic rearrangement of the methyl and bromo groups from **2a-ax**, forming **5a**, has a significantly higher barrier of 40.1 kcal/mol. The calculated  $\Delta G^\ddagger$  for TS-eq is consistent with our observations of a slow uncatalyzed transformation of **2a-e** to **3a-e** at room temperature in chloroform ( $t_{1/2} \approx 6$  days).

Both TS-eq and TS-ax are highly polarized, with two long C–Br bonds (>3.0 Å) and two short C–C bonds, and as such can be described as tight ion-pairs of a carbocation and bromide anion. Indeed, the bromine atom in these two TSs bears an almost full negative charge (−0.95 to −0.97 au, see SI). This is in stark contrast to classical type I dyotropic rearrangements of vicinal dibromides, where the C–Br bonds were calculated to be around 2.5–2.8 Å.<sup>8f</sup> It is known that delocalization of the formed  $\pi$  bond in the TSs of dyotropic rearrangements provides key stabilization.<sup>8d,e</sup> In the case of TS-eq, the large polarization causes the carbon backbone of the substrate to approach the geometry of a  $\pi\sigma$ -delocalized bisected cyclopropylcarbinyll (nonclassical) cation (vide infra).<sup>26,27</sup> This greatly stabilizes the  $\pi$  bond of the TS (in blue, Figure 3) and explains why TS-eq has such a low barrier compared to TS-ax, for which the carbon backbone has the geometry of a less-stabilized corner-protonated cyclopropane.<sup>28</sup>

Having established that the enantiospecific uncatalyzed reaction is very likely to operate through a concerted dyotropic rearrangement, we investigated the role of an external Lewis acid (Figure 4). Formation of **2a·ZnBr<sub>2</sub>** from the isolated reactants is favorable by 8.9 kcal/mol [see SI]. From this coordinated species, no concerted dyotropic transition states could be located; instead a stepwise mechanism is found.



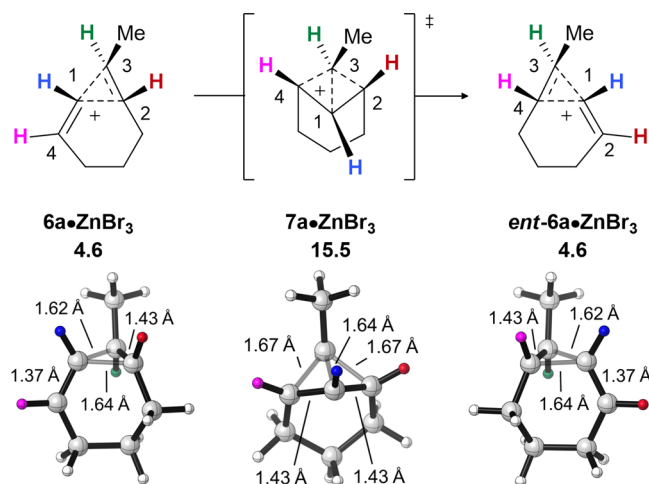
**Figure 4.** Calculated free energy profile for the stepwise transformation of **2a** to **3a**, catalyzed by ZnBr<sub>2</sub>. For the structure of **6a·ZnBr<sub>3</sub>**, the ZnBr<sub>3</sub><sup>−</sup> is hidden for clarity.

Ionization of the C–Br bond of complex **2a·ZnBr<sub>2</sub>** through TS 1 has a low barrier of 14.6 kcal/mol and leads to a contact ion-pair consisting of nonclassical cyclopropylcarbinyll cation **6a** and ZnBr<sub>3</sub><sup>−</sup>. From this intermediate, only 7.8 kcal/mol is required to reach TS 2, where the C–Br bond of **3a** is formed. These calculations are consistent with the much faster reaction observed when ZnBr<sub>2</sub> is used as Lewis acid, since the activation barrier is predicted to be almost 10 kcal/mol lower than in the uncatalyzed case (14.6 vs 25.2 kcal/mol). While some stepwise ionic dyotropic rearrangements are known, these were limited to intramolecular examples (e.g., dyotropic rearrangement of Himbert cycloadducts via a zwitterion).<sup>29,30</sup> The present mechanism is an unprecedented case of a stepwise formal dyotropic rearrangement proceeding through an ion-pair.

Ionization of the C–Br bond in TS 1 happens with simultaneous backside attack of the alkenyl group, analogous to an S<sub>N</sub>2 mechanism. Similarly, bromide attack in TS 2 occurs with release of the alkenyl group; therefore the C–Br bonds are broken and formed from the same face of **6a**, the structure of which is determined by the stereochemistry of **2a**. Thus **6a** is a *chiral* carbocation; however, even in the presence of Lewis acids such as ZnBr<sub>2</sub>, the reaction of **2d** to **3d** was shown to be perfectly enantiospecific. We performed additional calculations to investigate the possible mechanism of racemization of **6a**. It is now well established that cyclopropylcarbinyll cations<sup>26,27</sup> are in equilibrium with the related bicyclobutonium cations, with the latter being more stable for the parent C<sub>4</sub>H<sub>7</sub><sup>+</sup>.<sup>31,32</sup> For the bicyclic cyclopropylcarbinyll cation **6a**, the profile is much more complex. The lowest-energy path for the racemization of **6a** is through the *meso*-bicyclobutonium **7a**, which is a TS (instead of a minimum) on the potential energy surface of cation **6a** (Figure S).<sup>33</sup>

Once *chiral* cation **6a** is formed from the C–Br bond cleavage of **2a**, it requires an additional 10.9 kcal/mol of free energy to racemize through **7a·ZnBr<sub>3</sub>**, a bicyclobutonium ion-pair. In contrast, it only needs 7.8 kcal/mol to recombine with the ZnBr<sub>3</sub><sup>−</sup> counteranion to form the stable product **3a** through TS 2. Moreover, the latter reaction is not reversible, as **3a·ZnBr<sub>2</sub>** is 5.4 kcal/mol more stable than the starting complex. As such, there is a kinetic barrier to racemization in this system, allowing a stepwise enantiospecific rearrangement to occur.





**Figure 5.** Lowest-energy pathway for racemization of **6a•ZnBr<sub>3</sub>**. Free energies (kcal/mol) are relative to **2a•ZnBr<sub>2</sub>** (Figure 4). The  $\text{ZnBr}_3^-$  anions are hidden for clarity.

In summary, we have discovered an unanticipated ring contraction of bromocycloheptenes under mild conditions with remarkable regio- and stereochemistry. The ring contraction occurs via a double 1,2-migration of an alkene group and a bromide. DFT calculations show that the reaction proceeds through a nonclassical carbocation–anion pair; the  $\pi\sigma$ -delocalized bisected cyclopropylcarbanyl cation is crucial for the low activation barrier and enantiospecificity of the rearrangement. The reaction is concerted when uncatalyzed, presenting a rare type I dyotropic rearrangement of an alkene on a C–C stationary scaffold. In contrast, the reaction follows a stepwise mechanism under Lewis acid catalysis, and can be described as a formal dyotropic rearrangement. Our study also highlights how cations derived from chiral homoallylic halides may be productive intermediates in other enantiospecific reactions.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b00821.

Experimental procedures and characterization data, and data for computed structures (PDF)

NMR and chiral GC spectra (PDF)

X-ray crystallographic data for compound **3d** (CIF)

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<sup>#</sup>S.S.G. and P.A.C. contributed equally.

## Notes

The authors declare no competing financial interest.

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